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ON THE EFFECTS OF CHLOROFORM, ETHIDENE, AND ETHER ON BLOOD-PRESSURE: BEING THE THIRD PROVISIONAL REPORT OF THE COMMITTEE ON ANÆSTHETICS TO THE SCIENTIFIC GRANTS COMMITTEE OF THE BRITISH MEDICAL ASSOCIATION.

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THE Committee have been engaged since their last report,[1] chiefly in investigating the condition of the blood-pressure in animals under the influence of chloroform, ethidene, and ether.

In the report of a Committee[2] appointed by the Royal Medical and Chirurgical Society, to inquire into the uses and effects of chloroform, and published in the *Transactions* for 1864, vol. xlvii., there is a very excellent but brief record of the state of the blood-pressure under chloroform and ether. The instrument used in these experiments was the hæmadynamometer of Poiseuille, which consists of a U-shaped tube, with mercury in the bend. One limb of the tube was connected with the femoral artery, and the rise of the mercury in the opposite limb indicated the blood-pressure. By means of this instrument the Committee were enabled to report that on administering chloroform there is first a transient rise of the blood-pressure, after which there is a gradual but not a regular fall. They also noticed that when the force of the heart was reduced by the chloroform to the full extent, the respiration of fresh air was at once followed by a rise of the mercury. In regard to ether, it was found that the primary rise in pressure is greater and more constant than with chloroform, and that the depressing effect is very slight, or may be altogether absent.

In our experiments we have been able to amplify these results, and, by means of more perfect instruments, to obtain more exact

[1] *Journal of Anatomy and Physiology*, Pt. II. p 224.

[2] The members of this Committee were T. B. Curling, Thomas Bryant, Samuel Cartwright, Arthur Farre, George G. Gascoigne, George Harley, Prescott Hewett, F. W. Mackenzie, William Marcet, Charles H. Moore, James Paget, William O. Priestley, Richard Quain, Francis Sibson, R. Dundas Thomson, Charles West, Septimus W. Sibley, George W. Callender, John Birkett—Mr Clover assisting.

records. We have used a very complete kymograph, made by Rudolph Rothe of Prague,[1] by means of which the variations in the column of mercury produced by the pulsations in an artery are written on a sheet of blackened paper, which is carried round by a clock-work arrangement. A sheet of paper eight feet long is adapted to the machine, and as three or four lines of tracing can be taken at different levels on the same sheet, a continuous tracing may be obtained of 24, 32, or even more feet. But further, the sheets can be changed in a few seconds, and so it is possible to take tracings of almost any length.[2] The instrument has also appliances by which the time may be recorded in seconds, half-seconds, or otherwise, immediately beneath the tracing of the blood-pressure. Lastly, there are two arrangements by which the exact times of administering and of discontinuing an anæsthetic can be marked. In this way we have obtained records of experiments on rabbits and dogs, those on dogs being of much the greater value.

In the case of the rabbit there is one fact of considerable interest, which seems to be deducible from these records. When the animal is not fully under chloroform, any fresh administration causes the most remarkable variations of blood-pressure, with retardation of the heart's contractions. There is frequently a sudden dip in the pressure to the extent of 40 mm. out of a total of 110 mm., and in the next few contractions there is a very rapid rise up to the former level, to be succeeded by another sudden dip. This occurrence followed so uniformly in certain stages of chloroform narcosis, on every approximation of a sponge containing the agent even for a few seconds to the animal's muzzle, that it was regarded as probably reflex. This is rendered probable by the fact that ammonia vapour applied to the nostrils of a rabbit causes stoppage of the heart's action.[3] When chloroform is given continuously, these variations gradually cease, and there succeeds a regular and gradual fall of pressure down to zero if the agent is pushed. It was noticed

[1] See Dr M'Kendrick's *Outlines of Physiology*, p. 358.

[2] In one case, a tracing 150 feet long was obtained.

[3] See Professor Rutherford's paper in *Journal of Anatomy and Physiology*, vol. viii. p. 283. "Cause of the retardation of the pulse which follows artificial or voluntary closure of the nostrils of the rabbit."

that in one or two instances ethidene produced sudden variations in pressure similar to those of chloroform, but that ether did not. Our experiments were not fully prosecuted on rabbits in regard to the more permanent effects of these two agents; but it may be said in general that ether seemed to have no influence on blood-pressure, while ethidene reduced it to a considerable extent, but not to total extinction like chloroform.

Turning to our experiments on dogs, the very first observation made was an exceedingly striking one. The animal used was a black retriever, six or seven months old. Chloroform was given, and during deep anæsthesia a canula was introduced into the carotid and connected with the kymograph. By the time connection with the kymograph was established no chloroform had been given for about two minutes. On first making the connection the pressure registered 104 mm., which may be regarded as nearly normal. But now, without any fresh dose, the pressure suddenly fell to zero with a remarkable retardation of the heart. Each pulsation had a height of 9 mm.,[1] and a duration of a second and a half. After this the pressure rose with remarkable variations, equal to 13 to 16 mm., referable to the respiratory movements. It is to be remembered that the animal had at this time nearly recovered from chloroform, as evidenced by the high initial pressure, and this sudden fall of pressure is apparently reflex in character, the heart being perhaps more liable to such influences under the conditions present. A fresh administration of chloroform at this time led to a fresh variation of pressure somewhat resembling those already referred to in the case of rabbits. On continuing the administration, all irregular variations were abolished, and the pressure gradually fell, but the agent was not in this instance pushed very far. During recovery from this administration, 70 seconds after the chloroform had been removed, and when the pressure had risen to 66 mm., there was, without any apparent cause, an occurrence somewhat like that at the outset, but less in degree. The pressure fell to 20 mm., and the heart's pulsations became infrequent,

[1] It will be understood that the figures given represent the column of mercury raised, or the difference in level of the mercury in the two limbs of the U-shaped tube. This will always be double the distance from the point at which the mercury in the two limbs is level.

each pulsation taking one and a half seconds. This continued for six beats, when the pressure rose slowly to 100 mm., with recovery of the frequency of the pulsations.

Ether administered to this dog produced little effect on the pressure ; if anything, improved it. There was slight diminution of pressure when the animal was struggling and howling.

Ethidene was given while the animal was still to some extent under the influence of ether. The pressure gradually but very slowly fell, and under repeated doses reached a minimum of 20 mm. The agent being still continued, the pressure began to rise, and had reached 28 mm., when it was removed. Subsequently ethidene was again given, and after prolonged and constant use the pressure was brought down to 7 mm., when the administration was stopped. It should be noted that all this time the respiratory movements were uninterrupted.

The same dog was used for a further set of experiments, which were prosecuted after a short interval, during which the animal partially recovered.[1] The pressure at the beginning of this series registered 110 mm., and the variations of pressure with respiration were well marked. Chloroform being given, there was an immediate fall of pressure, with considerable variations and reduction in the frequency of the heart's pulsations. The pressure remained about 70 or 80 mm. for about half a minute, and then there was a very rapid fall, with great slowing of the pulsations till the heart almost ceased. There was an interval of three seconds between two of the pulsations, of nine seconds between the next two, and of six seconds between the next, the pressure in these intervals being *nil*. The chloroform was removed when this rapid fall occurred. During this period the respiration continued. The pulsations were now resumed, but between each pulsation the pressure was minus, and the pulsation only raised the mercury 10 mm. generally to the basement line, while the beats occupied about one and three-quarter seconds. After twenty-nine of these pulsations, the breathing stopped, while the pulsations went on regularly as before. After a few seconds, artificial respiration was used by alternately compressing

[1] During the whole of these experiments anæsthesia was complete from beginning to end, and the partial recovery referred to was indicated by a return of blood-pressure to the normal.

the chest and leaving it to expand. This being prosecuted for thirty seconds, spontaneous respiration was resumed, and the pulsations became more marked, having a rather higher excursion than before, but still returning to a pressure of zero between each two pulsations. This continued for about forty-two seconds, when the pressure began to rise, and this went on continuously till in one hundred and sixty seconds a height of 100 mm. was reached.

We have dwelt in some detail on this last experiment because we regard it as one of unusual interest and importance. It is to be remembered that this animal got chloroform in the usual way, by a cloth saturated with the agent being held over his mouth and nose. He received no overdose, and the administration only lasted seventy seconds. As bearing on at least one mode of death under chloroform, the relation of the heart's action to respiration is of particular significance. The blood-pressure is enormously reduced, and the pulsations have become so infrequent as to be virtually ineffective, yet respiration continues. But respiration stops forty seconds after the heart has resumed, the pulsations being still, however, so ineffective, that the pressure is even minus.[1] We believe that the legitimate inference to be drawn is that the stoppage of respiration was due not directly to the chloroform, the inhalation of which had ceased for about forty-eight seconds. It seems likely that the failure of the heart in the first instance, and the insufficiency of its subsequent pulsations, were the cause of the failure of respiration. In such a state of the circulation the respiratory centres would probably be insufficiently supplied with blood, and be consequently liable to cease acting. In this case, if death had occurred it would only apparently have been due to the failure of the respiration; the primary failure being that of the heart. To what extent this may apply to human cases we do not venture to speculate.

We now resume consideration of this set of experiments. The animal was allowed to recover considerably, and the pressure had reached 106 mm. when ethidene was administered. There was a slow but steady fall of pressure, the lowest point being reached

[1] That there was no fallacy here was determined by testing the instrument afterwards.

in about a hundred and twenty seconds, when the height was 36 mm. Continuing the administration, there was a slight rise up to 50 mm., when the administration was discontinued. During the administration, the cardiac pulsations were regular in frequency, with slight variations in the height of the waves, probably depending on respiration.

It will not be necessary to give our further experiments in such detail. In one set we kept up artificial respiration by means of the pump,[1] administering the anæsthetics by passing the air through a Wolff's bottle containing the respective agent. In these experiments chloroform promptly reduced the pressure, which began to recover almost immediately on its removal. On continuous administration, the pressure fell much more gradually than by the ordinary method, and the lowest point reached still represented a considerable pressure, about 65 mm. The initial pressure was 132 mm. Ethidene was begun at a pressure of 80 mm., the recovery from the chloroform depression being incomplete. After prolonged use there was a fall to 54 mm. On removal a gradual recovery ensued, which attained to 80 mm. Ether was then given, when again a slight fall in pressure ensued.

The next experiment is a somewhat interesting one, offering in a certain sense the converse of one already narrated. The same animal was used as in the last experiment; the tracheal tube was left in, and the animal breathed through it. The anæsthetics were administered by holding a cloth soaked with the agent over the mouth of the tube. Chloroform was given, and there was an almost immediate fall of pressure; but the fall was gradual, and in two hundred and thirty-four seconds had reached 28 mm., when the chloroform was stopped. The respiration ceased just after the chloroform had been removed. Artificial respiration was at once resorted to, but in spite of this the heart ceased beating twenty-one seconds after. It is remarked, however, that although there were no indications of the heart's pulsations in the tracing, the pressure was maintained at 28 mm., and it is just possible that there may have been slight pulsations too feeble to be recorded. The pause of the heart continued for

[1] The apparatus for artificial respiration used in the Physiological Laboratory, University of Glasgow, is the double-piston pump, made by Rudolph Rothe, of Prague, and figured in his price-list.

twenty-one seconds, and the pulsations were then resumed very feebly and irregularly. The pressure rose gradually to 46 mm., when a spontaneous respiration was given; then with long intervals spontaneous respirations were resumed. Artificial respiration was then stopped, as it was not required.

In this observation, it seems undoubted that the respiration failed first. The rapid failure of the heart is a remarkable circumstance, especially when the comparatively high pressure is considered. It is possible that the use of artificial respiration may have had to do with it. The respirations before they ceased were shallow, and though the air in the lungs was saturated with chloroform, little of it would find its way into the blood in the very limited respiratory movements. The introduction of artificial respiration would at first force the saturated air rapidly through the lungs, which would be vigorously inflated, and thus a large amount of chloroform would be introduced into the blood.

After the animal had recovered from this experiment ethidene was given. There was a fall of pressure, but, though administration was continued in frequently-repeated doses for nine minutes, the blood-pressure only fell to 38 mm., and there was no failure of respiration. Before the ethidene was removed the pressure had risen to 60 mm.

In this animal the pneumogastrics were now cut, and the observations repeated both with and without artificial respiration. It cannot be said that any essential difference was apparent in the results. The pressure fell both with chloroform and ethidene, but the fall was perhaps not so rapid or so great as under other circumstances. While artificial respiration was used, ethidene and chloroform were successively pushed to a very great extent, the Wolff's bottle being heated to facilitate the evaporation of the agents. Yet the blood-pressure was not reduced to the lowest even with this treatment, and in the case of ethidene it even began to rise under it. The effect on respiratory variations in pressure was remarked during these experiments In the case of ethidene, even when the agent was given to the fullest extent, the respiratory curve, though very much diminished, did not entirely disappear. In the case of chloroform the respiratory curve disappeared completely, and that

shortly after the commencement of administration. The cardiac pulsations in the case of chloroform became scarcely perceptible, the pressure, however, not falling below 40 mm. With ethidene in the same circumstances, the cardiac pulsations remained of nearly normal amplitude.

As a result of the whole set of experiments with this dog, it may be said that the heart showed throughout a remarkable state of vigour. It only exhibited signs of giving way on one occasion, and in that case the blood-pressure was maintained at a comparatively high position. On the other hand, respiration failed during the administration of chloroform very readily. In these respects the animal contrasts with the former one. It is quite obvious also that on these occasions when the breathing ceased the animal would almost certainly have died, but for the use of artificial respiration.

In some further experiments which we made with another dog, using Fick's kymograph,[1] a more remarkable result was obtained. Both respiration and heart had stopped under the use of chloroform, but by means of artificial respiration (by the pump) there was ultimate recovery, although the pulsations of the heart had ceased for a considerable time. In this case there could not be any feeble pulsations keeping up the circulation at a slow rate, as was supposed to be possible in a former case, because Fick's arrangement registers very accurately the slightest variations in the pressure produced by the heart's action. In the case of this dog also it was observed that several times, after a period of shallow respirations, the breathing stopped for a brief interval, the heart beating with considerable vigour. As respiration had ceased, no more chloroform was admitted to the blood, and after a time the respiratory movements returned. So much was this the case, that difficulty was experienced in killing this dog with chloroform; and this was only effected by administering it by artificial respiration after the spontaneous movements of respiration had ceased. By artificial respiration an additional quantity was introduced, and the heart soon succumbed.

These facts are of considerable importance, as they show the varying effects of chloroform in the same animal at different times. At one period respiration and the heart failed nearly

[1] The form shown in Dr M'Kendrick's *Outlines*, fig. 93, p. 357.

at the same time. At another respiration failed, and the heart, being still vigorous, was able to carry on the circulation till the chloroform had been sufficiently eliminated to allow of the recovery of the respiration.

The facts obtained from these researches seem to us to warrant the following conclusions:—

1. Both chloroform and ethidene administered to animals have a decided effect in reducing the blood-pressure, while ether has no appreciable effect of this kind.

2. Chloroform reduces the pressure much more rapidly and to a greater extent than ethidene.

3. Chloroform has sometimes an unexpected and apparently capricious effect on the heart's action, the pressure being reduced with great rapidity almost to *nil*, while the pulsations are greatly retarded, or even stopped. The occurrence of these sudden and unlooked-for effects on the heart's action seems to be a source of serious danger to life, all the more that in two instances they occurred more than a minute after chloroform had ceased to be administered, and after the recovery of the blood-pressure.

4. Ethidene reduces the blood pressure by regular gradations, and not, so far as observed, by these sudden and unexpected depressions.

5. Chloroform may cause death in dogs either by primarily paralysing the heart or the respiration. The variations in this respect seem to depend to some extent on individual peculiarities of the animals; in some the cardiac centres are more readily effected, in others the respiratory. But peculiarities in the condition of the same animal very probably have some effect in determining the vulnerability of these two centres respectively, and they may both fail simultaneously.

6. In most cases respiration stops before the heart's action; but there was one instance in which respiration continued while the heart had stopped, and only failed a considerable number of seconds after the heart had resumed.

7. The use of artificial respiration was very effective in restoring animals in danger of dying from the influence of chloroform. In one instance its prolonged use produced recovery even when the heart had ceased beating for a considerable time.

8. Under the use of ethidene there was on no single occasion

an absolute cessation either of the heart's action or of respiration, although they were sometimes very much reduced. It can therefore be said that, though not free from danger on the side of the heart and respiration, this agent is in a very high degree safer than chloroform.

9. These results confirm and amplify those stated in a previous report, to the effect that ethidene does not compromise the heart as does chloroform. By the method of experimentation then employed, the effect on the blood-pressure could not be determined, and altogether the results here obtained are more exact and unequivocal.

It may be added that, since last report, ethidene has been given to a number of patients of all ages, with results which may be described as satisfactory. Given freely at first, it produced anæsthesia as rapidly as chloroform, and the effect could readily be kept up by comparatively small subsequent doses. The only drawback is that in some cases it produced vomiting; but it is not determined that it does so more frequently than chloroform, over which it has the further advantage of producing less excitement, and being more agreeable to the patients.

Iso-butyl chloride was given to three patients, but it produced considerable excitement, and proved an imperfect anæsthetic. It has therefore been abandoned.

The Committee intend next directing their attention to the influence of anæsthetics on the pulmonary circulation, and to their action on various kinds of protoplasm.

The Committee will give an account of the previous history of ethidene chloride in the next number of this Journal.